CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 5, 2011
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	22-454
Applicant Name	GE Healthcare
Date of Submission	November 16, 2010
PDUFA Goal Date	January 14, 2011
Proprietary Name / Established (USAN) Name	DaTscan™ Ioflupane I 123 Injection
Dosage Forms / Strength	DaTscan is supplied in 10-mL glass vials containing 2.5 mL of solution; each mL contains 0.07 to 0.13 mcg ioflupane, 74 MBq (2 mCi) of iodine 123 as ioflupane I 123 at calibration time along with defined excipients. The recommended dose is 111 to 185 MBq (3 to 5 mCi) administered intravenously.
Proposed Indication(s)	DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.
Action/Recommended Action:	Approval/a postmarketing study (PMC) to assess: agreement of image results with clinical diagnoses following 3 years of follow-up among African-American patients with clinically uncertain Parkinsonian syndromes (PS).

Importantly, this is the third review cycle for this application. The original submission was on March 6, 2009 and a Complete Response letter was issued on September 8, 2009 (deficiencies related to need for package insert labeling update). The second review cycle began with the applicant's resubmission on October 26, 2009 and concluded with issuance of a Complete Response letter on December 22, 2009 in which the single deficiency related to the need to incorporate Controlled Substance text in the package insert. The reviews cited below pertain predominantly to the original cycle review period.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Phillip Davis, MD & Louis Marzella, MD, PhD (TL)
Statistical Review	Mark Levenson, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Sunday Awe, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Ravindra Kasliwal, PhD & Eldon Leutzinger, PhD
Microbiology Review	Bryan Riley, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Moon Choi, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	Lauren Iacono-Connors, PhD & Tejashri Purohit-Sheth, MD
CDTL Review	Louis Marzella, MD, PhD
OSE/DMEPA	Denise Baugh, PharmD & Todd Bridges, PharmD (TL)
OSE/DDRE	Kathryn O'Connell, MD, PhD & Claudia Karwoski, PharmD
Pediatric and Maternal Health	Jeanine Best, MSN, RN & Karen Feibus, MD (TL)
Project Manager	James Moore, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

On March 6, 2009, GE Healthcare submitted a New Drug Application (NDA) to support the marketing of DaTscan™ (^{123}I-ioflupane), a radiopharmaceutical imaging agent proposed for use in visualizing dopamine transporter protein (DAT) in the brain.

The current submission is the third review cycle for the drug, as outlined above. With the notification from DMEPA today that the proprietary name is acceptable and the container labels appropriate, all review concerns have been resolved. The overall regulatory background is notable for the following items:

During the original cycle:

- The application was assigned a priority review (as supported by neurologic consultation);

- The three DaTscan phase 3 studies had several atypical features which were discussed at an advisory committee that was held on August 11, 2009; the committee voted 11 to 2 to support a favorable risk to benefit determination for the drug;

- At least one phase 3 study (study 304) provided data sufficient to describe performance characteristics (strengths and limitations);

- The other two phase 3 studies provided collaborative findings;

- The overall DaTscan development program importantly contributed to the clinical assessment of the drug's efficacy in that:

  -*in vitro* autoradiography of human tissue confirmed DaTscan binding to DAT,

  -imaging "reads" were standardized as negative or positive in phase 3 studies in a manner proposed for market use,

  -imaging "reads" pertained to standard hot-spot anatomical visualization; specifically the radioisotope outlined the striatum as a readily recognizable anatomical structure,

  -imaging "reads" were read consistently among independent readers,

  -imaging read methods could be readily described in the package insert.

- No chemistry/manufacturing issues were identified during the original review cycle and all disciplines regarded the application as approvable except for statistics.

- The statistical reviewer did not regard the phase 3 study data as statistically persuasive to support approval of the drug;

- I agreed with the advisory committee and the clinical team that the totality of the nonclinical and clinical data were sufficient to support approval of DaTscan to assist in the evaluation of certain patients (as described in the final indication);

- A Complete Response letter was issued due to inability to resolve package insert text prior to the cycle termination date. Deficiencies pertained only to labeling.

During the second review cycle:

- The sponsor sufficiently responded to the labeling items identified at the conclusion of the original review cycle.

- Further review determined that DaTscan needed labeling modification to identify it as a schedule II narcotic because the active moiety is a derivative of cocaine. The review team acknowledged the sponsor's contention that abuse was not a

realistic consideration based upon the DaTscan dose, its presentation as well as its need to be handled by nuclear pharmacists.

- (b) (5)

- A Complete Response letter was issued based solely upon the need to have controlled substance text incorporated in the labeling.

During the current review cycle:

- The resubmission contains the proposed labeling (revised package insert and container labels), a safety update (no notable safety concerns are reported from non-USA post-marketing experience and an ongoing study), a copy of the non-USA labeling, a response to the previous two FDA requests for post-marketing studies (these two studies were not requirements and the sponsor's response is outlined below).

- The sponsor incorporates all requested labeling text, including the controlled substance information. As of today, all outstanding issues have been resolved.

- The sponsor proposes a survey-type of post-marketing commitment study to help estimate DaTscan performance characteristics among non-Caucasians (a population with very limited representation within the overall NDA database) and to compare the results for Caucasians. This survey-type proposal is based, in large, part upon feasibility considerations due to reports of a lower prevalence of Parkinsonian symptoms among non-Caucasians.

  -final clinical protocol submission date: December 31, 2011
  -clinical trial completion date: April 30, 2013
  -final trial report submission date: July 31, 2013

- The sponsor justified not performing a post-marketing study to examine the effect of Parkinsonian therapies upon DaTscan images. The justification included summary data that verified no effect of drugs commonly used to treat Parkinsonian symptoms.

- (b) (5) we plan to recommend approval of DaTscan as a controlled drug. All other issues have been resolved/the labeling describes the currently controlled nature of the drug.

Below is text largely excerpted from my original review memorandum.

During the original review, multiple findings necessitated modification of the proposed indication to that listed in the boxed header (at the top of this document). For example,

data were not available to verify that DaTscan imaged "functional neurons." Additionally, the review disclosed multiple data limitations within the three confirmatory clinical studies. For example, Study 304 (the most informative study) was extensively modified (10 protocol amendments) that fundamentally changed its original design. The other two clinical studies (301 and 003) had even more deficits. Nevertheless, Study 304 data were particularly strong in terms of the ability of the study to compare DaTscan image results to a reliable clinical diagnosis (based upon 3 years of follow-up after the DaTscan image). Additionally, the preclinical data were indisputable in terms of supporting the contention that DaTscan bound specifically to the human dopamine transporter (DaT) protein in the striatum.

The preclinical and clinical review teams supported approval of DaTscan. The statistical team pointed out the lack of statistical robustness within the confirmatory studies such that they regarded these studies as insufficient to support approval. The Advisory Committee voted 11 to 2 in support of a favorable risk-benefit profile for the drug. Overall, I regard the totality of data (particularly preclinical data and Study 304) as providing an acceptable risk-benefit profile for marketing. Post-marketing commitments were sought to obtain data from African Americans receiving DaTscan and to assess the potential interference with DaTscan imaging by dopaminergic drugs. As noted above the sponsor has supplied summary data indicating that commonly used anti-Parkinsonian drugs do not importantly change DaTscan results.

The indication for DaTscan ultimately reflected the strength of the supplied preclinical and clinical data. DaTscan may serve a particularly useful role in the evaluation of patients with clinically uncertain Parkinsonian Syndromes (PSs). PS have been associated with decreased dopamine neuroactivity within the striatum, coincident with loss of dopamine-secreting (dopaminergic) neurons and DaT. The PS diseases predominantly consist of multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and Parkinson's Disease. These conditions are, among other features, characterized by tremor. In contrast, the form of tremor identified as "Essential tremor" (ET) is not thought to be associated with loss of dopaminergic neurons and DaT. Hence, a reliable imaging test for DaT could assist the clinician in distinguishing PS from ET.

The DaTscan clinical program verified the usefulness of the test in distinguishing PS from ET based upon a single study (Study 304) that compared baseline DaTscan images to clinical diagnoses after three years of follow-up. This duration of follow-up was regarded as a reliable clinical diagnostic standard, particularly since it was formed by movement disorder specialists. A supportive study (Study 003) provided additional data describing the agreement between DaTscan images and baseline clinical diagnoses.

2. Background:

The active drug substance in DaTscan is ^{123}I-ioflupane, a cocaine derivative with affinity for the DaT. DaT has been shown to be prevalent within the striatum, a portion of the brain that consists of two major parts within each cerebral hemisphere, the caudate and putamen. The presence of DaT on the surface of dopaminergic neurons assists in the

recycling (uptake) of dopamine back into the neurons. Exploiting the DaT affinity of ^{123}I-ioflupane, the applicant proposed that injection of ^{123}I-ioflupane (DaTscan) into humans allowed visualization of the striatum on SPECT imaging and implicitly, the detection of abnormal distribution of DaT and/or dopaminergic neurons throughout the striatum.

Diagnostic radiopharmaceuticals (such as DaTscan) have specific regulations pertaining to their demonstration of safety and effectiveness (21 CFR 315). The regulations note that the effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indication. The regulations provide a list of potential indication categories and the efficacy expectations for each category. For example, to obtain a "biochemical" type of indication (as the applicant generally proposed for DaTscan), the regulations note that, "The claim...is established by demonstrating in a defined clinical setting, reliable measurement" of the biochemical process. The regulations also note that the usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status which may be provided by: (a) a diagnostic standard, (b) standards of demonstrated accuracy or (3) "established in another manner, e.g., patient follow-up." The DaTscan clinical program generally addressed a "biochemical" type of indication in which these regulatory expectations were addressed in the following manner (Table 1):

Table 1. Regulatory Characterization of DaTscan

Clinical Usefulness	• Study 304 used clinical follow-up as a comparator for DaTscan images; Follow-up extended over a 3 year period • Study 003 was a supportive study that compared DaTscan images to baseline clinical diagnoses
Reliability	• Data verified specificity of ioflupane binding to the human DaT (autoradiography of human brain slices with specific competition analyses) and *in vitro* binding assays of ioflupane to recombinant DaT • Study 304 also was a "defined clinical setting" that allowed a reliable estimate of agreement between DaTscan images and clinical diagnoses • Animal studies verified binding of radiolabeled ioflupane to striatum with displacement by DaT competitors

3. Chemistry, Manufacturing and Controls:

The original cycle Chemistry review was performed mainly by Dr. Ravindra Kasliwal. The microbiology review was performed by Dr. Bryan Riley. The reviewers verified acceptable manufacturing procedures and facility inspections also supported the approval of the application.

4. Nonclinical Pharmacology/Toxicology:

I concur with the original cycle conclusions reached by the Dr. Sunday Awe, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval. The pharmacology/toxicology provided some labeling recommendations which were incorporated into draft labeling. No post-marketing commitments were requested. The animal data were particularly robust in demonstrating that ioflupane binds specifically to the DaT within the striatum of animals. Autoradiography of human brain slices verified the specificity of ioflupane for DaT within the human brain.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the original cycle clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provided some recommendations for labeling which were incorporated into the draft labeling text. No outstanding issues were identified and no post-marketing commitments were requested.

The reviewer provided specific recommendations for certain pharmacology information within the labeling and these items were incorporated into the final labeling.

6. Clinical Microbiology:

The original cycle microbiology reviewer recommended approval and I concur with his findings.

7. Clinical/Statistical-Efficacy:

Dr. Phillip Davis provided the main clinical review and Dr. Mark Levenson provided the main statistical review and below I summarize the major clinical data.

Overall, three major clinical confirmatory clinical studies were submitted in the application, Studies 003, 304 and 301. Study 301 examined image results among patients with dementia while the other two studies examined patients with tremor. A supportive study (the Walker Study) was also supplied; this study compared DaTscan images to autopsy diagnoses of dementia. Hence, the development program focused upon two major areas: dementia and clinically uncertain PS.

The basis for potential use of DaTscan in PS was described in the introduction to this document. The basis for the potential use of DaTscan in dementia relates to the observation that Dementia with Lewy Bodies (a specific type of dementia) has been associated with loss of DaT while other types of dementia (e.g., Alzheimer's) generally are not associated with DaT loss.

a. Evaluation of patients with tremor:

The safety and efficacy of DaTscan were evaluated in two multicenter, single-arm studies (Study 304 and Study 003) that evaluated 287 adult patients with tremor. In the studies, DaTscan image outcomes were compared to a clinical diagnostic standard of "PS" or "non-PS". The clinical diagnostic standard for "PS" consisted of the following diagnoses: Parkinson's disease, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These three conditions have been associated with dopaminergic neurodegeneration and DaTscan imaging was not designed to distinguish among the conditions. The reference clinical diagnostic standard for "non-PS" consisted of an essential tremor (ET) diagnosis or other non-PS diagnosis. Both studies excluded subjects with concomitant medications known or suspected of interacting with striatal uptake of DaTscan. Three to 6 hours after DaTscan administration, subjects underwent SPECT imaging with a variety of multi-headed cameras or a multi-detector single-slice systems.

DaTscan images were evaluated by readers blinded to clinical information. Study 304 readers had no other role in patient assessment; Study 003 readers included site investigators. The clinical diagnostic standards were the clinical diagnoses established by a consensus panel of movement disorder specialists that evaluated data inclusive through 36 months of follow-up (Study 304) or the investigator-determined baseline clinical diagnosis (Study 003). Study 304 consisted of patients with early features of Parkinsonism; patients with features suggestive of MSA or PSP were excluded. Study 003 consisted of patients with clinically established diagnosis of PS (Parkinson's disease, MSA, PSP) or ET.

Table 2 shows the positive percent agreement and negative percent agreement of the DaTscan image results with the reference clinical diagnostic standard. Positive percent agreement represents the percent of patients with abnormal DaTscan images among all the patients with a clinical diagnostic reference standard of PS. The negative percent agreement represents the percent of patients with normal DaTscan images among the patients with a non-PS clinical diagnostic reference standard.

Table 2. Positive and Negative Percent Agreements for Studies 304 and 003

Reader	Positive percent agreement (95 % CI) (% patients with an abnormal DaTscan image among patients with PS)	Negative percent agreement (95 % CI) (% patients with a normal DaTscan image among patients with non-PS)
Study 304 (patients with early signs and/or symptoms of PS)		
Reader A, n = 102	78 (66, 87)	97 (83, 100)
Reader B, n = 99	78 (66, 87)	97 (83, 100)
Reader C, n = 101	79 (67, 88)	97 (83, 100)
Study 003 (patients with established diagnoses of PS or ET)		
Reader A, n = 185	93 (88, 97)	96 (81, 100)
Reader B, n = 185	97 (93, 99)	74 (54, 89)
Reader C, n = 185	96 (92, 99)	85 (66, 96)
Reader D, n = 185	92 (87, 96)	93 (76, 99)
Reader E, n = 185	94 (90, 97)	93 (76, 99)

b. Evaluation of patients with dementia:

Study 301 evaluated patients with various forms of dementia. The study compared DaTscan images to baseline clinical diagnoses, as well as clinical diagnoses after one year of follow-up. (b) (4)

The "Walker" study compared dementia diagnoses from autopsy histopathology to DaTscan images made many months prior to death. Within the "Walker" Study, clinical diagnoses were incorrect in 9/22 patients and DaTscan findings were incorrect in 4/22 patients. The small sample sizes as well as limitations within the histopathology diagnostic criteria were regarded by the FDA review team as important limitations to these data.

(b) (4)

8. Safety:

The most notable safety findings pertain to the non-USA post-marketing experience. DaTscan has been marketed in Europe since 2000. During this time hypersensitivity reactions have uncommonly been reported. These reactions generally consisted of rash and pruritus and either resolved spontaneously or following the administration of

corticosteroids and anti-histamines. The risk for hypersensitivity reactions was cited as a warning in the label. No serious adverse reactions were observed in the clinical trials and adverse reactions were uncommon (<1% of patients). Adverse reactions consisted of headache, nausea, vertigo, dry mouth or dizziness. These reactions were of mild to moderate severity.

The risk for thyroid uptake of radioactive iodine was highlighted as a warning within the DaTscan label and the label includes direction for administration of a thyroid uptake blocking agent to prevent thyroid accumulation of radioactive iodine.

The review team regarded labeling as a sufficient measure for risk management. No risk evaluation and mitigation strategy was regarded as necessary, a conclusion supported by the OSE/DRISK review.

Post-marketing Requirements (PMR): none

Post-marketing Commitments: a survey-type study to estimate DaTscan performance in non-Caucasians as compared to Caucasians.

9. Advisory Committee Meeting:

This application was presented to the Peripheral and Central Nervous System Advisory Committee on August 11, 2009. The committee voted (11 to 2) to conclude that the presented data represented a favorable risk to benefit profile for DaTscan.

10. Pediatrics:

Clinically uncertain PS was regarded as not applicable to the pediatric patient population and pediatric studies were waived.

11. Other Relevant Regulatory Issues:

Overall, the supplied data supports a favorable risk-benefit finding for the drug. The drug was associated with relatively few safety concerns and no unique risk management activities were regarded as necessary. In other matters, the FDA inspection of clinical sites disclosed no remarkable findings; financial disclosure expectations have been met.

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/s/

RAFEL D RIEVES
01/05/2011